IV. REMARKS

A. Specification Is Amended To Correct Minor Errors

Applicants amended the specification to correct typographical errors and clarify one passage. The specification, considered as a whole, provides support for the amendments. For example, the amendment at page 4 is supported by the specification considered as a whole, e.g., see page 6, lines 18-23.

B. Claims Are Amended In Accordance With Discussion At The Interview

Applicants amended their claims in accordance with the discussion at the personal interview kindly granted Applicants and their representative by Stephen L. Rawlings, Ph.D., the Examiner, his supervisor, Anthony C. Caputa, Ph.D. and Diana Dudash on June 25, 2003. Applicants appreciate the courtesy of that personal interview.

As agreed at the interview, Applicants amended their claims to recite a screening method for colorectoral cancer, or for a metastatic breast cancer in an individual who has been treated for primary breast cancer, and to the determination of the total TIMP-1 concentration in a plasma sample. Drs. Rawlings and Caputa agreed that such amendments would overcome the enablement rejections under 36 U.S.C. § 112, first paragraph, and indefiniteness rejections under 35 U.S.C. § 112, second paragraph, in the final Office Action. They also agreed that new claims 41 and 42 (added herein) also directed to screening for the colorectal cancer and the metastatic breast cancer (in an individual previously treated for a primary breast cancer), respectively, but based on the

measurement of a combination of total TIMP-1 and free TIMP-1, would be enabled and definite. Additional new claims 43-50 are directed to an aspect of the invention embraced by the heretofore-existing claims. Also see specification, as a whole, e.g., page 8, lines 1-7. Thus, none of the new claims introduce new issues, and Applicants respectfully request consideration thereof. Applicants provide below further rebuttal of the enablement and indefiniteness rejections, address all other issues in the final Office Action and other miscellaneous items discussed at the interview.

C. Restriction Requirement

It was stated that claims 6-12 and 20-26 were withdraw from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention, because, allegedly, there is no allowable generic or linking claim. Applicants were requested to cancel the non-elected claims or take other appropriate action. Office Action, pages 2 and 12.

Applicants continue to traverse this rejection and respectfully request that claims 6-12 and 20-26 be rejoined and examined with the other claims in the application in view of the agreement reached at the interview. Applicants also respectfully submit that, since claims 6-12 are dependent from claim 1, and it was agreed at the interview that claim 1 would be in condition for allowance if it is amended as set forth above, claim 1 is an allowable claim generic to claims 6-12. Similarly, claims 20-26 depend from claim 15, which also is in condition for allowance as agreed at the interview. Thus, claim 15 is an allowable claim generic to claims 20-26.

In the event that the Examiner does not agree with Applicants' arguments, but

otherwise agrees that all claims (other than claims 6-12 and 20-26) are in condition for allowance, Applicants hereby authorize the Examiner to cancel by the Examiner's amendment claims 6-12 and 20-26 to place the entire application in condition for allowance. In such an event, claims 6-12 and 20-26 are cancelled without prejudice and with the reservation of all of the Applicants' rights to pursue the subject matter of such claims in any related applications, such as continuations, divisionals or continuation-in-part applications.

D. Abstract of the Disclosure is Properly Placed

Applicants were required to submit a separate page containing the abstract with a request that the page be properly placed and entered because the abstract (submitted in a response to the previous Office Action) was not printed on a separate appropriately numbered page. Office Action, page 2. Applicants have complied with this request.

In particular, Applicants include herewith under Tab 1, page 47, containing the abstract of the claimed invention.

E. Applicants Appreciate Indication of Withdrawal of Claim Objections and Claim Rejections

Applicants appreciate the indication in the Final Office Action that objections of claims 4, 5, 13, 14, 18, 19, and 27-37 were withdrawn and rejections of claims 1-3 and 15-17 under 35 U.S.C. §112, second paragraph, were also withdrawn.

F. Claims 1, 4, 5, 13-15, 18, 19, 27-36 And 38-40 Were Enabled By The Specification Prior To The Amendment Hearin. The Amended Claims Continue To Be Enabled

Claims 1, 4, 5, 13-15, 18, 19, 27-36 and 36-40 were rejected Under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable a person skilled in the art to which the invention pertains or with which it is most nearly connected to make and/or use the invention. The reasons set forth in the November 9, 2001 Office Action were relied upon for this rejection. Final Office Action, page 3. Several different reasons were additionally included in the Final Office Action for this rejection. Applicants present below arguments rebutting all of such bases, as also discussed at the interview.

At the outset, Applicants wish to point out that the claimed invention is directed to a screening method for a metastatic breast cancer (in an individual who has been treated for primary breast cancer) or for a colorectal cancer in an individual. This is an important aspect of the invention (as also discussed at the interview).

One of the basis for the enablement rejection was that, allegedly, there is no factual evidence in the specification leading a skilled artisan to a reasonable conclusion that the concentrations of TIMP-1 in bodily fluids of patients "... correlates positively with the presence or the probable incidence of cancer in those patients". Final Office Action, pages 5 and 7. Reiterating Applicants' arguments at the interview, such evidence is presented by Applicants in their specification considered as a whole, e.g., in Examples 5 and 4

The sample of patients discussed in example 5 consisted of a large number of colorectal cancer patients carrying the disease at different stages. Example 5 (page 29) shows that total TIMP-1 levels are significantly higher in colorectal cancer than in non-malignant colon disorders, such as inflammatory bowel disease (IBD), ulcerative colitis

and Crohn's disease ($p<0.00001$, see a paper published by Applicants, Holten-Andersen et al. "Total Levels of Tissue Inhibitor of Metalloproteinases 1 In Plasma Yield High Diagnostic Sensitivity and Specificity in Patients with Colon Cancer", *Clinical Cancer Research*, Vol. 8, 156-164, January 2002) (copy enclosed in the herewith-filed Information Disclosure Statement IDS, discussed below). Reiterating discussion at the interview most, if not all, of the data included in the application was published in the Holten-Andersen paper (or article). These data demonstrate the specificity of the screening method for colorectal and secondary mammae (i.e., breast) cancer as compared to healthy blood donors since, at high specificity substantially all healthy individuals are correctly identified by the method with very few false positives (false indications of colorectal cancer or secondary mammae cancer).

Furthermore, in example 4, which is based on the same sample of patients as described above, it is demonstrated that the sensitivity and specificity of TIMP-1 as a screening marker is clearly significant in early stages (Dukes A+B) of colon cancer (fig. 14). This would lead to more people being diagnosed at early stages of the disease. As is known in the art, based on the use of the FOB-test (faecal occult blood test), screening for colorectal cancer which results in early detection would most probably lead to higher life expectancy.

In example 4, directed to colorectal cancer, mean total TIMP-1 value for colorectal cancer patients was 141.1 µg/ L, for colon patients it was 158.6 µg/L and for rectal patients 126.3 µg/L. In contrast, for healthy blood donors, the median TIMP-1 level was 88.6 µg L. Specification, pages 26-27. Applicants also concluded that

"[T]there was a highly statistical difference in the total plasma TIMP-1 values between the colorectal cancer patients and the healthy blood donors". Specification, page 27, lines 2-3. As Dr. Nils Brünner pointed out at the interview, p values reported in the Holten-Andersen article ($p< 0.0001$) indicate a high significance of the differences between TIMP-1 level for colorectal cancer patients and healthy blood donors. *Id.*, page 159.

Another reason for this rejection was that "because the range of values of the concentrations of TIMP-1 in the bodily fluid of patients known to have cancer substantially overlaps the range of the values of the concentrations of TIMP-1 in the bodily fluid of individuals considered healthy and disease-free, the discriminatory value of the concentration of TIMP-1 in the bodily fluids, which might delineate one group from the other, is obscured." Final Office Action, page 5.

Reiterating the discussion at the interview, as with any screening method, an overlap may exist, and it is largely due to the presence of a very small proportion of data points at either extreme of a range of values of a selected marker. A comparison of median values of TIMP-1 between healthy donors and diseased individuals provides a meaningful indication of the significance of the differences in the TIMP-1 values between the healthy and diseased individuals. When such median values are compared, the significance of the differences is clear and it clearly informs persons of ordinary skill in the art how to delineate a group of potentially healthy from a group of potentially diseased individuals. For instance, in Example 4, the median TIMP-1 level for healthy individuals was 88.6 µg/L and for all colorectal patients 141.1 µg/L.

Similarly, in Example 11, the median total TIMP-1 level in metastatic breast cancer patients was 236 µg/L, as compared to a median of 62 µg/L in healthy female donors. See specification, page 35.

During the interview, Dr. Rawlings requested that Applicants address the teaching of the abstract contained in Oberg et al., "Limited Value of Preoperative Serum Analysis of Matrix Metalloproteinases (MMP-2, MMP-9) and Tissue Inhibitors of Matrix Metalloproteinases (TIMP-1, TIMP-2) in Colorectal Cancer", *Anticancer Research* 20: 1085-1092 (2000). The portion of Oberg relied upon (identified in the November 9, 2001 Office Action) was the statement in the abstract that "analyses of the total concentration of TIMP-1 in serum samples acquired from colorectal patients reveal that TIMP-1 is of limited value for tumor staging and prognosis (Abstract)". November 9, 2001 Office Action, page 9. As Dr. Brünner stated during the interview, Oberg's observation is based on analysis of serum (rather than plasma). Additionally, Oberg's observation was directed to "tumor staging and prognosis" (Oberg et al., Abstract, last sentence), while Applicants' invention is a screening method.

It was also asserted that the threshold value used to discriminate between an individual "... having cancer from an individual not having cancer is arbitrary". Office Action, page 6. Applicants, reiterating discussion at the interview, respectfully traverse this assertion.

As pointed out above, Applicants' invention is a screening method for colorectal cancer or for secondary breast cancer. Applicants teach that, once an individual is determined as likely to have either one of those cancers, the individual

> "... should be referred for further examination. If a cancer is found, the patient could be offered surgery, radiation or adjuvant or anti-neoplastic therapy aiming at curing the patient of cancer".

Specification, page 5, lines 22-24. Thus, Applicants' method is not directed to the diagnosis of an individual with cancer. The discriminating value of the total concentration of TIMP-1 will be selected by a clinician based on a level of sensitivity or level of specificity acceptable to the clinician.

In determining the discriminating value distinguishing individuals with a high versus low probability of having colorectal cancer, a person skilled in the art has to predetermine the level of specificity. The ideal screening test is a test that has 100% specificity, i.e., detects all non-diseased individuals and therefore no false positive results, and 100% sensitivity, i.e., detects all diseased individuals and therefore no false negative results. However, due to biological diversity no method can be expected to be 100% sensitive without including a substantial number of false positive results.

The chosen specificity determines the percentage of correctly identified negative cases (i.e., disease free) and false positive cases that can be accepted in a given study/population and by a given institution. By decreasing specificity, an increase in sensitivity is achieved (see fig. 13). One example is a specificity of 95% which will result in a 5% rate of false positive cases, or 95% of true negatives. With a given prevalence of 1% of colorectal cancer in a screening population, a 95% specificity for a 100 individuals screening sample means that 5 individuals will undergo further physical examination in order to detect one (1) cancer case if the sensitivity of the test is 100%.

Therefore, a person skilled in the art would chose the level of specificity which is

considered acceptable in a given case. He (or she) will then turn to one of Figures 5a, 6 or 7 and find the corresponding discriminating value by drawing a vertical line from the specificity percentage, the x-axis (1-specificity) up to the interception point of the data line. From there he (or she) can draw a horizontal line towards the y-axis and read the discriminating value of the TIMP-1 concentration corresponding to the chosen specificity.

That person will then find the sensitivity related to the chosen specificity (at the resulting discriminating value obtained from Fig. 5a, 6 or 7) by using Figs. 13, 14 or 15. This procedure was used by the inventors and published in their Holsten-Andersen article (discussed above), see table 3. This table shows the corresponding sensitivity when specificity was chosen to be 95% or 98%.

The issue of sensitivity vs. specificity can be explained based on figure 13. The figure is a graphical illustration of the relationship between specificity and sensitivity for plasma TIMP-1 in patients with colon or rectal cancer as compared with blood donors. On the x-axis, the specificity is delineated as 1-specificity, this means that 100% specificity will be at the intersection with the y-axis. On the y-axis is depicted sensitivity.

It was also asserted that Applicants failed to disclose the discriminatory value in the specification of the concentration of TIMP-1 which would enable the invention to be used with a high degree of specificity for identification of patients having cancer. Thus, it was alleged "that a skilled artisan would necessarily have to first determine which discriminating value should be used to have reasonable expectation of success in

practicing the claimed method to screen members of a population and identify individuals having, or at risk of having cancer", and "... to have a reasonable expectation of successfully determining whether an individual has or will have cancer, the practitioner ... will need to use a threshold value that most assuredly reveals the presence of cancer in the individual, but since the specification does not teach which value ... can be used in practicing the claimed methods to accomplish the objectives recited in the preamble of claims 1 and 15, the skilled artisan would first need to determine the discriminatory value of the threshold that will provide the required specificity." Office Action, page 7.

Reiterating the discussion at the interview, and the agreement reached, the claimed invention is directed to a screening method. Based on Applicants' specification and knowledge of persons skilled in the art, the discriminating value can be easily determined by a clinician based on his or her choice of selectivity and specificity.

G. Claims Prior to This Amendment Were Definite. Amended Claims Continue to be Definite.

Claims 1,4, 5, 13-15, 18, 19, 27-36 and 38-40 were rejected for indefiniteness under 35 U.S.C. § 112, second paragraph. One of the reasons for this rejection was the use of the phrases "a method for determining whether an individual is likely to have gastrointestinal cancer" and "or a method for determining whether a patient who has been treated for primary breast cancer is likely to have metastatic breast cancer." It was stated that it was not clear if the claimed invention is a method for determining whether an individual will develop gastrointestinal or metastatic breast cancer or if it is a

method for determining that an individual already has gastrointestinal or metastatic breast cancer, i.e., a method for diagnosing gastrointestinal or metastatic breast cancer. Office Action, pages 8 and 9. As discussed above, and at the interview, Applicants' claimed invention is directed to a screening method, as explained in the specification, e.g., see page 4, lines 6-11 and page 5, lines 21-24, and the claims reflect that.

The same claims were also rejected as indefinite for the presence of the phrase "a parameter *representing* the total concentration of TIMP-1." Office Action, page 9. Applicants continue to assert that their claims prior to this amendment were definite for all of the reasons set forth in the Amendment Under 37 C.F.R. § 1.111 filed on March 11, 2002. The amended claims continue to be definite.

The claims were also rejected due to the presence of the term "high" in claims 1 and 15 because it was a relative term, which rendered them indefinite. Office Action 9. For all of the reasons presented before in the Amendment Under C.F.R. § 1.111, the term "high" did not render the claims indefinite. Nonetheless, in the interest of advancing prosecution, Applicants amended the claims to remove that term. The amended claims continue to be definite.

Another ground for the indefiniteness rejection asserted in the Office Action was the presence of the term "a discriminating value". Office Action, page 10. It was asserted that the discriminating value can vary depending on the pre-selected variables of specificity and sensitivity and therefore it is "... still unclear what discriminatory value must be used [to] discriminate an individual having or likely to have cancer and an individual not having or unlikely to have cancer." Office Action, page 10. Applicants

agree with the Examiner that the discriminating value can vary, and it is determined by the level of sensitivity (or specificity) that a person of ordinary skill in the art would select in practicing the claimed invention for his or her particular screening procedure. It was agreed at the interview that this term is not indefinite, since persons of ordinary skill in the art will readily understand from the specification how to select that value and therefore would understand the metes and bounds of the claimed invention.

It was also asserted that the claims were indefinite due to the recitation of "a predetermined specificity and/or a predetermined sensitivity" in conjunction with the term "high". Office Action, page 10. Applicants continue to maintain that their claims, prior to the amendments herein, were definite. Nonetheless, the amended claims (which do not contain the term "high") continue to be definite.

H. Claims In The Prior Amendment Found Support In The Specification. The Amended Claims Continue to Satisfy 35 U.S.C. § 112

Claims 1, 4, 5, 13-15, 18, 19, 27-36 and 38-40 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not described in the specification, due to the recitation of "other than blood serum". It was alleged that the specification failed to provide proper and sufficient antecedent basis for this recitation. Office Action, page 11. Applicants respectfully disagree since it is well established that an omission of an element in a claim from a number of elements recited in the specification does not eliminate support in the specification for the claimed invention. Nonetheless, Applicants amended their claims to expedite prosecution, and the amended claims continue to be supported by the specification.

Claims 1, 4, 5, 13-15, 18, 19, 27-36, and 38-40 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite due to the recitation of the process step "whereby the **likelihood** that said individual is **likely** to have [...] cancer is determined in view of the preambles of the claims, which, allegedly, were incongruous with the text recited in the positive process steps. It was suggested that this rejection can be overcome by amending claim 1 to recite "whereby the likelihood that said individual has or will have gastrointestinal cancer is determined". Office Action, pages 11-12. While Applicants continue to maintain that their claims prior to the amendment herein were definite, they nonetheless adopted the Examiner's kind suggestion and amended the claims as stated in the Office Action. The herein-amended claims continue to be definite.

I. Miscellaneous

During the interview the Examiners asked Applicants to determine if the following text at page 35, lines 20-21 of the specification was correct:

> "The mean total TIMP-1 level measured in the 19 breast cancer patients was 292± 331 µg/L (median: 236 µg/L)."

Figure 20 is a graphical representation of the data discussed in this portion of the specification. Applicants wish to advise that the results are highly influenced by one value of >1600 µg/ml and considering this as an outlier would result in an estimated mean level of 220+/-80 µg/ml (median 221 µg/ml) for the remaining 18 breast cancer patients.

During the interview, Dr. Rawlings requested that Applicants submit two articles by some of the inventors named in this application:

A. Mads Holten-Andersen et al., "Measurement of the Noncomplexed Free Fraction of Tissue Inhibitor of Metalloproteinaeses 1 in Plasma by Immunoassay", *Clinical Chemistry* 48:8, 1305-1313 (2002); and

B. Mads Holten-Andersen et al. "Total Levels of Tissue inhibitor of Metalloproteinases 1 in Plasma Yield High Diagnostic Sensitivity and Specificity in Patients with Colon Cancer", *Clinical Cancer Research*, Vol. 8, 156-164, January 2002.

Applicants are submitting these articles with the enclosed Information Disclosure Statement.

J. Information Disclosure Statements

Applicants respectfully request an indication that the attached Information Disclosure Statement has been considered and that the Information Disclosure Statement submitted on June 28, 2002, has also been considered. Applicants respectfully request that copies of the Forms PTO-1449 with the Examiner's initials in the left column be returned to them to indicate consideration of the documents cited in the two respective IDSs. Applicants also wish to point out that one of the documents cited in the IDS of June 28, 2002, is a co-pending Application No.: 10/117,030, which is a continuation-in-part of this patent application, which was briefly discussed at the interview.

V. REQUEST FOR ALLOWANCE

Applicants submit that for all of the reasons set forth above, all claims are in condition for allowance, an indication of which is solicited. In the event any outstanding issues remain, Applicants would appreciate the courtesy of a telephone call to the undersigned counsel to resolve such issues in an expeditious manner and place the application in condition for allowance.

If any fees are necessitated by the filing of this Amendment, please charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,
HUNTON & WILLIAMS

Date: July 10, 2003

Stanislaus Aksman
Registration No. 28,562

1900 K Street, N.W., Suite 1200
Washington, D.C. 20006-1109
Ph. (202) 955-1500
Fax (202) 778-2201